prior to November 29, 2000, Applicant is entitled to amend the Priority Claim as set forth in 37 CFR 1.78(a)(2)(ii)(B) without fee payment requirements. Applicant notes that the originally asserted priority claim included all of the patent applications present in the currently asserted priority claim, however a typographical error in the previously asserted priority chain prevented the Patent Office from recognizing the complete priority claim. Applicant has thoroughly reviewed the priority claim to correct for the typographical error. As mentioned above, Applicant has included a patent application family tree to make correction of the priority claim clearer and easier for the Patent Office to follow.

AMENDMENTS TO THE SPECIFICATION

In order to simplify the amendment process, Applicant has amended the specification to include paragraph numbers. Accordingly, a **Substitute Specification** is being submitted herewith in two forms: 1) a marked up copy showing all corrections and deletions; and 2) a clean copy with all corrections included without markings.

Both versions of the **Substitute Specification** include amendments to the specification made previously in the amendments filed on September 20, 2001 and August 2, 2002. A statement under 37 CFR § 1.125(b)(1) is also provided verifying that the **Substitute Specification** includes no new matter.

CLAIMED SUBJECT MATTER AND INVENTORSHIP

Upon careful review of the subject matter in the claims of the instant application, Applicant has recognized that the inventorship of the instant application must be corrected. Of the originally named inventors, Stephen J. Garger has recognized that he is not a co-inventor of the currently claimed subject matter and has signed a statement under 37 CFR § 1.48(a) to assert the removal of his name as an inventor. Further, two inventors named in

Laurence Grill, have recognized that they are co-inventors of the claimed subject matter, and also, Gregory Pogue has recognized that he is also a co-inventor of the claimed subject matter. Accordingly, Robert Erwin, Laurence Grill and Gregory Pogue have signed statements under 37 CFR § 1.48(a) verifying that they are inventors of the currently claimed subject matter. In accordance with 37 CFR § 1.48(a), a new Declaration has also been executed to include all of the correct inventors and payment of the required fee under 37 CFR § 1.17(i) from Applicants deposit account is authorized, as set forth in the accompanying FEE TRANSMITTAL form.

Applicant has also added new dependent claims 3-8. Consequently, claims 2-8 are now pending. Applicant respectfully requests re-consideration of claim 2 in light of the arguments provided hereinbelow and consideration of new claims 3-8.

REQUEST FOR CONTINUING EXAMINATION UNDER 37 CFR § 1.114

Applicant has filed herewith a Request For Continued Examination along with authorization for payment of fee of $375, via charge to Applicant's deposit account. Applicant has fewer than 500 employees and is therefore entitled to small entity status and corresponding reduced fees.

INFORMATION DISCLOSURE STATEMENT

Applicant is also filing herewith, an Information Disclosure Statement in order to introduce several references that support the arguments set forth below with respect to the rejection under 35 USC § 102(b) in the Office Action mailed September 17, 2002. Further, in a counterpart PCT application, Applicant recently received a Search Report that included additional reference also being submitted with the accompanying Information Disclosure

PRIORITY APPLICATION SERIAL NUMBERS 07/219,279 and 07/363,138

Applicant previously informed the Examiner of the subject matter of two previously filed patent applications: US Application Number 07/219,279, filed July 15, 1998, entitled "SYNTHESIS OF AN ESTERASE OF LIPASE BY NON-CHROMOSOMAL TRANSFORMATION OF A HOST", (now abandoned); and US Application Number 07/363,138 filed June 8, 1989, entitled "SYNTHESIS OF STEREOSPECIFIC ENZYME BY NON-CHROMOSOMAL TRANSFORMATION OF HOST" (now abandoned), both of which are included in the corrected priority claim of the instant application. The inventors for these two priority applications are Robert Erwin and Laurence Grill, who are also inventors of the claimed subject matter of the instant application.

In the Office Action, a request was made for mention of the invention in earlier filed applications that are part of Applicant's priority claim. In the first filed case, SN 07/219,279, expression of lysosomal enzymes such as lipase is described beginning on page 19, line 14 through the end of page 28. In the second filed case, SN 07/363,138, there are numerous portions of the text that refer to expression of lysosomal enzymes such as lipase, including Examples 18 and 19 on pages 66-68. Copies of these two commonly assigned patent applications accompany this amendment.

REJECTION UNDER 35 USC § 103

In the Office Action, reference was made to rejections under 35 USC § 103, however, no specific rejections were introduced. Rather, reference was made to inventorship of the claimed invention.

Inventorship and the priority claim of the instant application have been corrected, and copies of the specification of two priority applications have been provided to verify the subject matter described therein.

REJECTION UNDER 35 USC § 102(b)

The Examiner has rejected claim 2 under 35 USC § 102(b) over the Goodman reference, US 4,956,282, as allegedly teaching expression of active mammalian proteins in plant cells, either in culture or under cultivation. Applicants respectfully traverse the rejection. Goodman does not describe expression of lysosomal enzymes in plants. The generalized discussion of the desirability to express heterologous proteins in plants found in the "Introduction" section in Goodman relates to the ability to use a particular and very specific "cassette" for heterologous gene expression. The examples given, and the claims, describe interferon production and the use of the specific cassette comprising interferon.

In respect to the feasibility of plant as bioreactors, it should be mentioned that while it is an attractive general idea, a skilled artisan, before undertaking a project to express a specific heterologous protein product in plant, would consider numerous objective criteria by which lysosomal enzyme expression in plants does not appear reasonably guaranteed to succeed. For example, a heterologous protein product that is either much smaller or much larger than most host protein products may be considered more vulnerable to degradation, and particularly vulnerable to proteinase degradation. For discussion of protein degradation in plants, applicants attach hereto two publications on the subject, for the convenience of the examiner. See Hondrean and Vierstra, *Curr. Opin. Biotech* 1: 147-151 (1992), and Vierstra, Ann. *Rev. Plant Physiol. Mol. Biol.* 44: 385-410 (1993) (copies provided with the accompanying I.D.S.).

Generally, while it may be hoped that a mammalian gene would fold properly in a plant environment, there is no reasonable certainty of this result. The plant intracellular environment may differ from the intracellular environment where the protein is normally expressed. This would have particular consequence for protein folding. For example, a fish antigen protein expressed was shown completely unstable when expressed in plants at normal temperatures. See Kenward et. al., *Plant Mol. Biol.* 23: 377-85 (1993), a copy of which is included with the I.D.S. for the convenience of the Examiner. Further yet, the processing of the heterologous protein product in plants may produce an altered structure, or lead to miscompartamentalization, or be processed in low yields. For examples of heterologous proteins modified by their in planta processing see Lee and Raikhel, *Brazilian J. Med. Biol. Res.* 28: 743-50 (1995) (copy accompanies the I.D.S.).

However, for the present invention, proper processing and folding is a critical point. Lysosomal enzymes have market potential as an orphan drug for enzyme replacement therapy, in addition to their use in molecular biology. If the plant lysosomal enzymes are structurally different from mammalian lysosomal enzymes, their activities and/or its specificity may be altered. Such alteration would reduce their marketability, particularly in regard to its use as an orphan drug for enzyme replacement.

In fact, others teach that expression of heterologous DNA in a plant is unpredictable. Fischhoff et al., WO 90/10076 pp. 1-13, (see I.D.S) state that expression of a heterologous gene in transformed plant cells might be so inefficient as to be without utility, due to incomplete transcription of the gene due to premature transcription termination, due to

polyadenylation of mRNA; instability of the cytoplasmic mRNA; inefficient translation of the cytoplasmic mRNA; or instability of the protein due to its susceptibility to plant proteinases. Nevertheless, the applicants have achieved expression of lysosomal enzymes in plants, and further at levels of commercial usefulness.

There is no suggestion in either Goodman, or in the other citations, to combine the teachings in regard to lysosomal enzyme expression. The very existence of a heterologous expression system for lysosomal enzyme in the fungus *Aspergillus flavus* (see US Patent No. 5,082,778 with I.D.S.) teaches away from the more expensive engineering and production in plants as a commercial venue, and the unlikelihood that levels of expression will ever be high enough and the properties retained for use in commercial production. There were objective and serious criteria by which a proposal for expression of lysosomal enzyme in plant was suspect: will it be stable; will it affect host metabolism; will it fold properly? Based on the above explanations, the applicants believe that production in plants was not the obvious avenue to pursue commercialization of a lysosomal enzyme.

Applicant respectfully asserts that the application is now in condition for allowance. However, should the Examiner have any questions or identify any further issues that need to be resolved, she is invited to contact the undersigned directly in the hopes that any remaining issues can be resolved expeditiously. The undersigned's direct phone number is: 707-469-2313.

Respectfully submitted,

Date: Jun. 30, 2003

John C. Robbins
Agent for Applicant(s)

REPLACEMENT PAGE WITH ALL CLAIMS, INCLUDING CURRENT CLAIM 2 AND NEW CLAIMS 3-8

2. A recombinant expression construct comprising a nucleotide sequence encoding a lysosomal enzyme and a promoter that regulates the expression of the nucleotide sequence in a plant cell.

3. A recombinant expression construct as set forth in claim 2, wherein said recombinant expression construct is a recombinant viral expression construct.

4. The recombinant expression construct as set forth in claim 2, wherein the lysosomal enzyme is lipase.

5. The recombinant expression construct as set forth in claim 3, wherein the lysosomal enzyme is lipase.

6. The recombinant expression construct as set forth in claim 2, wherein the lysosomal enzyme is alpha galactosidase.

7. The recombinant expression construct as set forth in claim 3, wherein the lysosomal enzyme is alpha galactosidase.

8. The recombinant expression construct as set forth in claim 2, wherein the lysosomal enzyme is glucocerebrosidase.

PRIORITY CLAIM OF US PATENT APPLICATION S.N. 09/626,127